

Cutaneous *Mycobacterium haemophilum* Infection Involving the Upper Extremities: Diagnosis and Management Guidelines

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PRACTICE POINTS

- *Mycobacterium haemophilum* infections typically occur on the extremities of immunosuppressed patients.
- Acid-fast bacilli staining may be negative.
- Mycobacterial cultures may take up to 6 weeks for growth.
- Prolonged triple-antibiotic therapy and lowering of immunosuppression is ideal treatment.

Mycobacterium haemophilum is a nontuberculous organism that commonly manifests as cutaneous lesions and subcutaneous nodules in immunosuppressed adults. Because *M haemophilum* infection is rare, the epidemiology, reservoir, and mode of transmission remain largely unknown. Infection presents a challenge to the dermatology community because it is infrequently suspected and commonly misidentified, resulting in delayed diagnosis. We discuss 3 cases of cutaneous *M haemophilum* infection to better understand clinical presentation, diagnosis, and management.

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Infection with *Mycobacterium haemophilum*, a rare, slow-growing organism, most commonly presents as ulcerating cutaneous lesions and subcutaneous nodules in immunocompromised adults.¹ The most common clinical presentation in adults includes cutaneous lesions, nodules, cysts, and papules, with signs and symptoms of erythema, pain, pruritus, and drainage.² Disseminated

disease states of septic arthritis, pulmonary infiltration, and osteomyelitis, though life-threatening, are less common manifestations reported in highly immunocompromised persons.³

Infection with *M haemophilum* presents a challenge to the dermatology community because it is infrequently suspected and misidentified, resulting in delayed diagnosis. Additionally, *M haemophilum* is an extremely fastidious organism that requires heme-supplemented culture media and a carefully regulated low temperature for many consecutive weeks to yield valid culture results.¹ These features contribute to complications and delays in diagnosis of an already overlooked source of infection.

We discuss the clinical presentation, diagnosis, and treatment of 3 unusual cases of cutaneous *M haemophilum* infection involving the upper arms. The findings in these cases highlight the challenges inherent in diagnosis as well as the obstacles that arise in providing effective, long-term treatment of this infection.

Case Reports

Patient 1—A 69-year-old woman with a medical history of a single functioning kidney and moderate psoriasis managed with low-dosage methotrexate presented with an erythematous nonhealing wound on the left forearm that developed after she was scratched by a dog. The pustules, appearing as bright red, tender, warm abscesses, had been present for 3 months and were distributed on the left proximal and distal dorsal forearm (Figure 1A). The patient reported no recent travel, sick contacts, allergies, or new medications.

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A shave biopsy was initially obtained. Swab specimens were sent for bacterial, fungal, and mycobacterial culture following discontinuation of methotrexate. Initial histopathologic analysis revealed aggregates of histiocytes and multinucleated giant cells within the dermis, surrounded by infiltrates of lymphocytes and neutrophils (Figure 2), consistent with a dermal noncaseating granulomatosis. Acid-fast bacilli (AFB), periodic acid–Schiff, Gram, and Grocott-Gomori methenamine–silver stains were negative for pathogenic microorganisms. There was no evidence of vasculitis.

Despite negative special stains, an infectious cause was still suspected. Oral doxycycline monohydrate 100 mg twice daily, oral fluconazole 200 mg daily, and econazole cream 1% were prescribed because of concern for mycobacterial infection and initial growth of *Candida parapsilosis* in the swab culture.

A punch biopsy also was performed at this time for both repeat histopathologic analysis and tissue culture. Follow-up appointments were scheduled every 2 weeks. Staining by AFB of the repeat histopathologic specimen was negative.

The patient demonstrated symptomatic and aesthetic improvement (Figure 1B) during consecutive regular follow-up appointments while culture results were pending. No lesions appeared above the left elbow and she had no lymphadenopathy. Results of blood chemistry analyses and complete blood cell count throughout follow-up were normal.

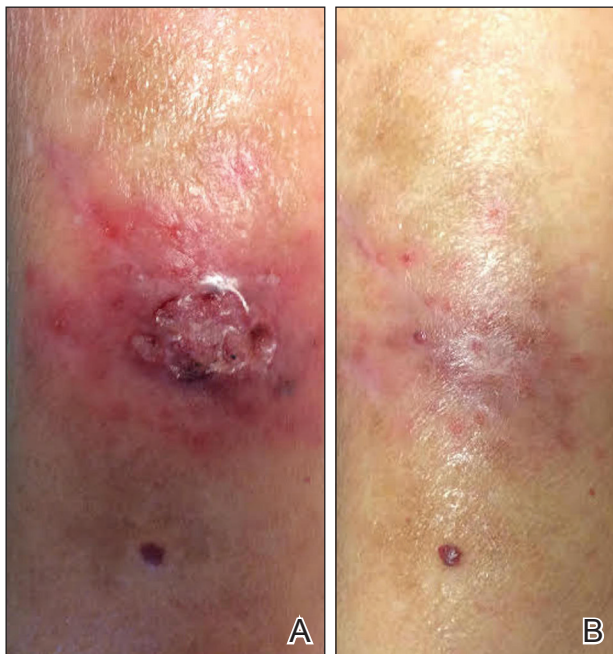


FIGURE 1. A, *Mycobacterium haemophilum* infection before treatment (patient 1). B, Clinical improvement was notable after 2 weeks of therapy with topical econazole, oral doxycycline, and oral fluconazole, and before starting triple-drug therapy.

The final tissue culture report obtained 7 weeks after initial presentation showed growth of *M haemophilum* despite a negative smear. The swab culture that initially was taken did not grow pathogenic organisms.

The patient was referred to an infectious disease specialist who confirmed that the atypical mycobacterial infection likely was the main source of the cutaneous lesions. She was instructed to continue econazole cream 1% and was given prescriptions for clarithromycin 500 mg twice daily, ciprofloxacin 500 mg twice daily, and rifampin 300 mg twice daily for a total duration of 12 to 18 months. The patient has remained on this triple-drug regimen and demonstrated improvement in the lesions. She has been off methotrexate while on antibiotic therapy.

Patient 2—A 79-year-old man with a medical history of chronic lymphocytic leukemia, basal cell carcinoma, and squamous cell carcinoma presented with a nonhealing, painful, red lesion on the left forearm of 1 week's duration. Physical examination revealed a violaceous nontender plaque with erosions and desquamation that was initially diagnosed as a carbuncle. The patient reported a similar eruption on the right foot that was successfully treated with silver sulfadiazine by another physician.

Biopsy was performed by the shave method for histologic analysis and tissue culture. Doxycycline 100 mg twice daily was prescribed because of high suspicion of infection. Histologic findings revealed granulomatous inflammation with pseudoepitheliomatous hyperplasia, reported as squamous cell carcinoma. A second opinion confirmed suspicion of an infectious process; the patient

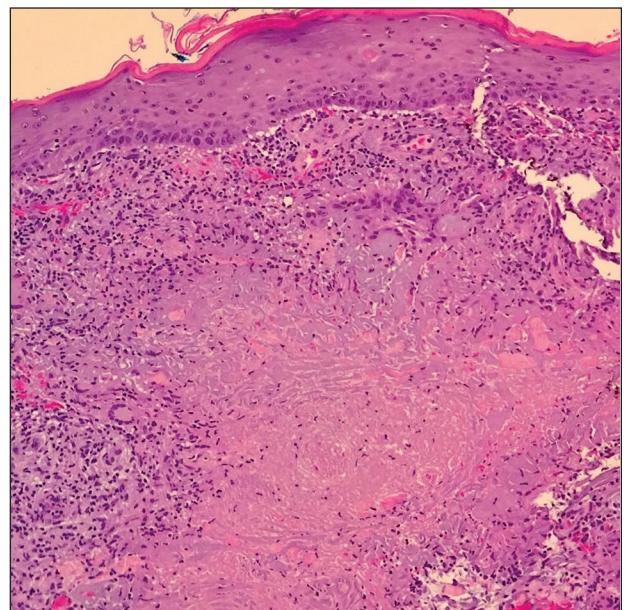


FIGURE 2. Histologic evaluation of a shave biopsy specimen revealed a dense dermal inflammatory infiltrate of multiple caseating granulomas surrounded by lymphocytes, histiocytes, and multinucleated giant cells (patient 1)(H&E, original magnification $\times 40$).

remained on doxycycline. During follow-up, the lesion progressed to a 5-cm plaque studded with pustules and satellite papules. Multiple additional tissue cultures were performed over 2 months until “light growth” of *M haemophilum* was reported.

The patient showed minimal improvement on tetracycline antibiotics. His condition was complicated by a photosensitivity reaction to doxycycline on the left and right forearms, hands, and nose. Consequently, triamcinolone was prescribed, doxycycline was discontinued, and minocycline 100 mg twice daily and ciprofloxacin 500 mg twice daily were prescribed.

Nine months after initial presentation, the lesions were still present but remarkably improved. The antibiotic regimen was discontinued after 11 months.

Patient 3—A 77-year-old woman with a history of rheumatoid arthritis treated with methotrexate and abatacept as well as cutaneous T-cell lymphoma treated with narrowband UVB radiation presented to the emergency department with fever and an inflamed right forearm (Figure 3A). Initial bacterial cultures of the wound and blood were negative.



FIGURE 3. A, *Mycobacterium haemophilum* infection before treatment (patient 3). B, Clinical improvement was notable after 3 weeks of triple-drug therapy with azithromycin, rifampin, and ethambutol.

The patient was treated with vancomycin and discharged on cephalexin once she became afebrile. She was seen at our office the next week for further evaluation. We recommended that she discontinue all immunosuppressant medications. A 4-mm tissue biopsy for hematoxylin and eosin staining and a separate 4-mm punch biopsy for culture were performed while she was taking cephalexin. Histopathologic analysis revealed numerous neutrophilic abscesses; however, Gram, AFB, and fungal stains were negative.

Arm edema and pustules slowly resolved, but the eschar and verrucous plaques continued to slowly progress while the patient was off immunosuppression. She was kept off antibiotics until mycobacterial culture was positive at 4 weeks, at which time she was placed on doxycycline and clarithromycin. Final identification of *M haemophilum* was made at 6 weeks; consequently, doxycycline was discontinued and she was referred to infectious disease for multidrug therapy. She remained afebrile during the entire 6 weeks until cultures were final.

While immunosuppressants were discontinued and clarithromycin was administered, the plaque changed from an edematous pustular dermatitis to a verrucous crusted plaque. Neither epitrochlear nor axillary lymphadenopathy was noted during the treatment period. The infectious disease specialist prescribed azithromycin, ethambutol, and rifampin, which produced marked improvement (Figure 3B). The patient has remained off immunosuppressive therapy while on antibiotics.

Comment

Clinical Presentation and Diagnosis—*Mycobacterium haemophilum* is a rare infectious organism that affects primarily immunocompromised adults but also has been identified in immunocompetent adults and pediatric patients.² Commonly affected immunosuppressed groups include solid organ transplant recipients, bone marrow transplant recipients, human immunodeficiency virus–positive patients, and patients with rheumatoid arthritis.

The infection typically presents as small violaceous papules and pustules that become painful and erythematous, with progression and draining ulceration in later stages.² In our cases, all lesions tended to evolve into a verrucous plaque that slowly resolved with antibiotic therapy.

Due to the rarity of this infection, the initial differential diagnosis can include infection with other mycobacteria, *Sporothrix*, *Staphylococcus aureus*, and other fungal pathogens. Misdiagnosis is a common obstacle in the treatment of *M haemophilum* due to its rarity, often negative AFB stains, and slow growth on culture media; therefore, tissue culture is essential to successful diagnosis and management. The natural reservoir of *M haemophilum* is unknown, but infection has been associated with contaminated water sources.¹ In one case (patient 1), symptoms developed after a dog scratch; the other 2 patients were unaware of injury to the skin.

Laboratory diagnosis of *M haemophilum* is inherently difficult and protracted. The species is a highly fastidious and slow-growing *Mycobacterium* that requires cooler (30°C) incubation for many weeks on agar medium enriched with hemin or ferric ammonium citrate to obtain valid growth.¹ To secure timely diagnosis, the organism's slow agar growth warrants immediate tissue culture and biopsy when an immunocompromised patient presents with clinical features of atypical infection of an extremity. *Mycobacterium haemophilum* infection likely is underreported because of these difficulties in diagnosis.

Management—Although there are no standard guidelines for antibiotic treatment of *M haemophilum*, the current literature recommends triple-drug therapy with clarithromycin, ciprofloxacin, and rifamycin for at least 12 to 24 months.²

Upon clinical suspicion of an atypical *Mycobacterium*, we recommend a macrolide antibiotic over doxycycline, however, because this class of agents maintains broad coverage while being more specific for atypical mycobacteria. Although an atypical *Mycobacterium* was suspected early in the presentation in our cases, we discourage immediate use of triple-agent antibiotic therapy until laboratory evidence is procured to minimize antibiotic overuse in patients who do not have a final diagnosis. Single-agent therapy for prolonged treatment is discouraged for atypical mycobacterial infections because of the high risk of antibiotic resistance. Therapy should be tailored to the needs of the individual based on the extent of dissemination of disease and the severity of immunosuppression.^{1,2}

Additionally, underlying disease that results in immunosuppression might necessitate treatment reevaluation (as occurred in our cases) requiring cessation of immunosuppressive drugs, extended careful monitoring, and pharmacotherapeutic readjustment through the course of treatment. The degree to which antibiotics contribute to eradication of *M haemophilum* is unknown; therefore, it is recommended that long-term antibiotic use and treatment aimed at recovering the immunocompromised state (eg, highly active antiretroviral therapy in a patient with AIDS) be implemented.²

Conclusion

Our 3 cases of *M haemophilum* infection involved the upper extremities of immunosuppressed patients older than 65 years. This propensity to affect the upper extremities could possibly be due to the lower temperature required for growth of *M haemophilum*. Initial histopathologic study showed granulomatous and neutrophilic infiltrates, yet histopathologic specimens from all 3 patients failed to display positive AFB staining, which delayed the initial antibiotic choice. In all cases, diagnosis was made by tissue culture after swab culture failed to grow the pathogen. Furthermore, the 3 cases took approximately 6 weeks to achieve final identification of the organism. Neither clinical lymphadenopathy nor systemic spread was noted in our patients; immunosuppression was discontinued when possible.

Mycobacterium haemophilum is an uncommon but potentially life-threatening infection that should be suspected in immunocompromised adults who present with atypical cellulitis of the extremities. The ultimate diagnosis often is delayed because the organism grows slowly (as long as 8 weeks) in tissue culture. For that reason, empiric antibiotic treatment, including a macrolide, should be considered in patients with disseminated or severe infection or critical immunosuppression and in those who do not demonstrate improvement in symptoms once immunosuppressants are withheld. A prolonged course of multiple-drug antibiotic therapy has proved to be effective for treating cutaneous infection with *M haemophilum*.

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ERRATUM

Due to a submission error, the article "The Impact of Diet on Psoriasis" (*Cutis*. 2019;104[suppl 2]:7-10) stated the incorrect academic degree for one of the authors. The byline should read:

Albert G. Wu, MS; Jeffrey M. Weinberg, MD

The article has been corrected online at www.mdedge.com/dermatology.

The staff of *Cutis*® makes every possible effort to ensure accuracy in its articles and apologizes for the mistake.